SHORT COMMUNICATION

Premorbid vulnerability and disease severity impact on Long-COVID cognitive impairment

Viviana Cristillo[1] · Andrea Pilotto[1] · Stefano Cotti Piccinelli[1] · Giulio Bonzi[1] · Antonio Canale[2] · Stefano Gipponi[1] · Michela Bezzi[3] · Matilde Leonardi[4] · Alessandro Padovani[1] · the Neuro Covid Next Study group

Abstract

Background Cognitive deficits have been increasingly reported as possible long-term manifestations after SARS-CoV-2 infection.

Aims In this study we aimed at evaluating the factors associated with cognitive deficits 6 months after hospitalization for Coronavirus Disease 2019 (COVID-19).

Methods One hundred and six patients, discharged from a pneumology COVID-19 unit between March 1 and May 30 2020, accepted to be evaluated at 6 months according to an extensive neurological protocol, including the Montreal Cognitive Assessment (MoCA).

Results Abnormal MoCA scores at 6 months follow-up were associated with higher pre-hospitalization National Health System (NHS) score (Duca et al. in Emerg Med Pract 22:1–2, 2020) (OR 1.27; 95% CI 1.05–1.6; $p = 0.029$) and more severe pulmonary disease expressed by the Brescia-COVID Respiratory Severity Scale (Duca et al. in Emerg Med Pract 22:1–2, 2020) (BCRSS > 1OR 4.73; 95% CI 1.53–14.63; $p = 0.003$) during the acute phase of the disease.

Discussion This longitudinal study showed that the severity of COVID-19, indicated by BCRSS, and a complex score given by age and premorbid medical conditions, expressed by NHS, play a major role in modulating the long-term cognitive consequences of COVID-19 disease.

Conclusions These findings indicate that the association of age and premorbid factors might identify people at risk for long-term neurological consequences of COVID-19 disease, thus deserving longer and proper follow-up.

Keywords COVID-19 · Cognitive functions · Long-COVID · Neurology

Introduction

Since the global pandemic of COVID-19 began on March 1st, 2020, neurological complications of patients during the acute phases have been largely described in single series and multi-center studies [1, 2].

With the growing number of patients affected by COVID-19, several reports claimed for possible neurological long-term consequences of COVID-19. Persistent neurological complaints include mild symptoms, like headaches, loss of smell and taste, tingling sensations, dizziness, and severe fatigue; more specifically, cognitive impairment, memory, and attention deficits have been increasingly reported as possible short- and long-term manifestations after SARS-CoV-2 infection [3] It is still unclear whether the effects of SARS-CoV-2 on the brain are indirect (mediated by oxygen starvation of the brain and/or the body's extreme inflammatory

✉ Viviana Cristillo
viviana.cristillo@gmail.com

1 Department of Clinical and Experimental Sciences, Neurology Unit, Clinica Neurologica, University of Brescia, P.le Spedali Civili 1, 25123 Brescia, Italy

2 Department of Statistical Sciences, University of Padova, Padova, Italy

3 Respiratory Unit, ASST Spedali Civili di Brescia, Brescia, Italy

4 Neurology, Public Health, Disability Unit-Fondazione IRCCS Istituto Neurologico Carlo Besta, Milan, Italy

response in severely affected patients) or direct (mediated by virus invasion in the brain), or both [4–6].

In this longitudinal study, we aim at evaluating the factors associated with cognitive deficits 6 months after hospitalization for COVID-19. We specifically hypothesize that premorbid vulnerability and older age play a major role in predicting long-term cognitive sequalae of SARS-Cov-2 infection.

Materials and methods

This observational cohort study included all adult patients (≥ 18 years old) admitted at the Pneumology Ward, ASST Spedali Civili Hospital, Brescia (Italy), for respiratory complications of SARS-CoV2 infection, from March 1 to May 31. Out of 201 patients hospitalized for COVID-19, a sample of 106 patients accepted to be evaluated at 6 months from discharge through a full clinical and neurological examination, including the Montreal Cognitive Assessment (MoCA). Patients with anamnestic premorbid cognitive impairment ($n = 5$) or dementia ($n = 3$) were excluded. An abnormal MoCA score was considered for values under 2 standard deviations from the mean score obtained in a similar age and education sample.

Epidemiological, demographical, and clinical data were collected during the interview and extracted from medical records using standardized anonymized data collection forms. Premorbid comorbidities and general health conditions were assessed by the Cumulative Illness Rating Scale (CIRS) [7] and by the National Health Service (NHS) Covid-19 Decision Support Tool [8], a complex score obtained by the sum of 3 different domains, naming age, clinical frailty scale, and comorbidity. Hospitalization data included the severity of COVID-19 disease, classified according to the quick Sequential Organ Failure Assessment (qSOFA) and the Brescia-COVID Respiratory Severity Scale (BCRSS), an algorithm using patient examination features along with the need for escalating levels of respiratory support (low-flow/high-flow oxygen therapy, intubation) to suggest treatment recommendations [9]. More specifically, the patients included in this study were stratified according the BCRSS in mild and moderate, with a score of 0 and > 1, respectively. Furthermore, the follow-up evaluations were performed by neurologists and all data were imputed and checked by four physicians (VC, AP, SCP, and NZ). Patients with signs and symptoms occurred during SARS-CoV2 infection and lasted for more than 12 weeks, not explained by an alternative diagnosis, were identified as affected by "Long-COVID" syndrome, according to NICE guidelines (2020).

The Neuro-COVID Next study was approved by the local ethics committee of ASST Spedali Civili di Brescia Hospital (NP 4067, approved 08.05.2020).

Statistical analysis

Continuous and categorical variables are reported as median with interquartile range and n (%), respectively. Differences between patients with and without cognitive difficulties were compared by Wilcoxon–Mann–Whitney test or Fisher's exact test where appropriate. To explore the risk factors associated with cognitive impairment, univariable logistic regression model was implemented, including the following predictors: age, sex, premorbid CIRS, premorbid NHS, O2 therapy needed, and COVID-19 severity. The MoCA scores were adjusted for the effect of age and educational levels [10]. A two-sided $p < 0.05$ was considered statistically significant. Data analyses were carried out using SPSS software (version 24.0).

Results

From a sample of 168 consecutive patients, 106 (mean age 64.9 years, 26.7% female) were evaluated at 6 months according to an extensive medical and neurological protocol, including the Montreal Cognitive Assessment (MoCA). Table 1 highlights the factors associated with abnormal age- and education-adjusted MoCA scores ($n = 18$, 18.2%) [10]. Patients with abnormal scores exhibited higher premorbid vulnerability NHS score (OR 1.27; 95% CI 1.05–1.6; $p = 0.029$) and more severe pulmonary disease (BCRSS > 1OR 4.73; 95% CI 1.53–14.63; $p = 0.003$), with higher prevalence of patients requiring O2 treatment (100% vs. 77.1%; $p = 0.024$). Conversely, the two groups did not differ for age (70.3 vs 64.0 $p = 0.085$) and sex distribution (F% 44.4% vs. 22.9%, $p = 0.061$); more specifically, as considered the gender, the borderline p value is most likely an effect of the small size sample, thereby lack of statistical significance. The severity of COVID-19 and premorbid NHS score were confirmed as the only predictors of long-term cognitive deficits surviving in age- and sex-adjusted logistic regression model (Exp(B) = 1.27, $p = 0.04$ and Exp(B) = 4.73, $p = 0.007$, respectively). The predictive value for both variables was confirmed in models including and excluding age/ CIRS ($R2 = 0.19$ and $R2 = 18$, respectively), highlighting the importance of complex effect due to interaction between age and comorbidity, as expressed by NHS. Specifically, patients with both high premorbid vulnerability (NHS > 8) and moderate to severe COVID-19 disease (BCRSS > 1) exhibited a 5.84 increased risk of cognitive deficits (95% CI 1.87–18.27) compared to patients with mild respiratory disease (BCRSS < 1) and a lower vulnerability (NHS < 8); the logistic exhibited similar.

Table 1 Demographic and clinical factors associated with abnormal MoCA score

	Normal MoCA ($n = 83$)	Abnormal MoCA ($n = 18$)	p value	OR
Demographic and clinical characteristics				
Age, years	64.0 (53.9–71.6)	70.3 (63.3–77.2)	0. 085	
Sex, female	19 (22.9%)	8 (44.4%)	0.061	2.69 (CI 0.93–7.79)
mRS pre	0.00 (0.0–1.0)	1.00 (0.0–1.0)	0.123	
CIRS severity index pre-hospitalization	1.31 (1.15–1.46)	1.46 (1.21–1.61)	0.188	
NHS at admission (median value)	6.0 (4.0–7.0)	8.0 (5.0–8.25)	0.029	
NHS at admission > 8 (%)	18 (21.7%)	10 (35.7%)	0.007	1.27 (CI 1.005–1.6)
qSOFA at admission	0.00 (0.0–1.0)	0.00 (0.0–1.0)	0.135	
BCRSS at admission (median value)	0.00 (0.0–1.0)	1.00 (1.0–1.0)	0.003	
BCRSS at admission > 1 (%)	39 (47.0%)	15 (83.3%)	0.008	4.73 (CI 1.53–14.63)
BCRSS at discharge	0.00 (0.0–0.0)	0.00 (0.0–0.0)	0.481	
Low-flow oxygen treatment	64 (77.1%)	18 (100%)	0.024	1.28 (CI 1.14–1.44)
Non-invasive ventilation	15 (83.3%)	3 (16.7%)	0.704	1.31 (CI 0.32–5.27)
Total days of O_2 therapy	4.00 (1.0–10-0)	7.00 (2.0–11.25)	0.179	
NHS > 8 + BCRSS > 1	10 (12.0%)	8 (44.4%)	0.003	5.84 (CI 1.87–18.27)

BCRSS Brescia-COVID Respiratory Severity Scale, *CIRS* cumulative illness rating scale; *mRS* modified ranking scale; *qSOFA* quick Sequential Organ Failure Assessment

*p values were calculated by Mann–Whitney test or Fisher's exact test, as appropriate

Discussion and conclusions

This longitudinal study indicates that premorbid conditions play a major role in modulating the long-term consequences of COVID-19 disease. Recent data coming from larger surveys indicating age as key predictor of long-COVID [11–13]; of interest, age alone was not a good predictor of long-term cognitive deficits in our sample. This might indicate that older subjects are at higher risk of long-COVID only when premorbid vulnerability interacts with the severity of COVID-19 infection. Although the mechanisms underlying long-term central nervous system involvement are still unclear, these preliminary findings suggest that long-term cognitive deficits might represent part of the spectrum of long-COVID. Of interest, we included only subjects who did not reported any previous neurological disease or syndromes (including encephalopathies or encephalitis) during the acute phases of the disease. Conversely, we found that 18.2% of non-neurological patients exhibited abnormal age- and education-adjusted MoCA score—a percentage definitively higher compared with the expected value in the Italian general population, identified with 11%, considering both borderline and pathological performances [10]. For this, larger and longer clinical follow-up are definitively needed in order to better characterize the nature and progression of cognitive decline in patients with COVID-19, as we only observed subtle to mild deficits with no impact in activities of daily living. The main limitation of this study was the unavailability of premorbid cognitive assessment, although we accurately excluded subjects with cognitive impairment before hospitalization. Other important limitations were the small sample size and the lack data of asymptomatic and more severe COVID-19 patients that definitely need to be evaluated in larger on-going studies.

Limitations notwithstanding, this study highlighted for the first time that long-term cognitive deficits are predicted by the complex interaction between premorbid vulnerability and COVID-19 severity in hospitalized patients.

Declarations

Ethical approval All procedures performed in these studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. This study was approved by the local ethics committee of ASST Spedali Civili di Brescia Hospital (NP 4067, approved 08.05.2020).

Consent to participate Informed consent was obtained from all individual participants included in this study.

Consent for publication The authors affirm that human research participants provided informed consent for publication of the article.

References

1. Ellul MA, Benjamin L, Singh B et al (2020) Neurological associations of COVID-19. Lancet Neurol 19:767–783. https://doi.org/10.1016/S1474-4422(20)30221-0
2. Benussi A, Pilotto A, Premi E et al (2020) Clinical characteristics and outcomes of inpatients with neurologic disease and COVID-19 in Brescia, Lombardy Italy. Neurology 95:e910–e920. https://doi.org/10.1212/WNL.0000000000009848
3. Cristillo V, Pilotto A, Piccinelli SC et al (2021) Age and subtle cognitive impairment are associated with long-term olfactory dysfunction after COVID-19 infection. J Am Geriatr Soc. https://doi.org/10.1111/jgs.17296
4. Lucchese G, Floel A (2020) Molecular mimicry between SARS-CoV-2 and respiratory pacemaker neurons. Autoimmun Rev 19:102556. https://doi.org/10.1016/j.autrev.2020.102556
5. Pezzini A, Padovani A (2020) Lifting the mask on neurological manifestations of COVID-19. Nat Rev Neurol 16:636–644. https://doi.org/10.1038/s41582-020-0398-3
6. Zhou Z, Kang H, Li S et al (2020) Understanding the neurotropic characteristics of SARS-CoV-2: from neurological manifestations of COVID-19 to potential neurotropic mechanisms. J Neurol 267:2179–2184. https://doi.org/10.1007/s00415-020-09929-7
7. Parmelee PA, Thuras PD, Katz IR et al (1995) Validation of the cumulative Illness Rating Scale in a geriatric residential population. J Am Geriatr Soc 43:130–137. https://doi.org/10.1111/j.1532-5415.1995.tb06377.x
8. Peter Foster BS, Rovnick N. (2020) NHS 'score' tool to decide which patients receive critical care. Financial Times
9. Duca A, Piva S, Foca E et al (2020) Calculated decisions: brescia-COVID respiratory severity scale (BCRSS)/algorithm. Emerg Med Pract 22:1–2
10. Santangelo G, Siciliano M, Pedone R et al (2015) Normative data for the Montreal Cognitive Assessment in an Italian population sample. Neurol Sci 36:585–591. https://doi.org/10.1007/s10072-014-1995-y
11. Huang C, Huang L, Wang Y et al (2021) 6-month consequences of COVID-19 in patients discharged from hospital: a cohort study. Lancet 397:220–232. https://doi.org/10.1016/S0140-6736(20)32656-8
12. Sudre CH, Murray B, Varsavsky T et al (2021) Attributes and predictors of long COVID. Nat Med. https://doi.org/10.1038/s41591-021-01292-y
13. Writing Committee for the CSG, Morin L, Savale L et al (2021) Four-month clinical status of a cohort of patients after hospitalization for COVID-19. JAMA 325:1525–1534. https://doi.org/10.1001/jama.2021.3331
14. National Institute for Health and Care Excellence (2020) COVID-19 rapid guideline: managing the long-term effects of COVID-19. National Institute for Health and Care Excellence: Clinical Guidelines. London, UK